FORM PTO-1390
(REV. 5-93)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER
6727/0J367US0

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

09/856417

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IL99/00619	November 17, 1999	November 18, 1998

TITLE OF INVENTION

VAGINALLY ADMINISTRATABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME

APPLICANT(S) FOR DO/EO/US

Azariah JOSSIFOFF

Applicant herewith submits to the United States Designated/Elected office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S. C. 371.

3. [] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S. C. 371 (b) and PCT Articles 22 and 39 (1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S. C. 371 (c) (2))
   a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [X] A translation of the International Application into English (35 U.S. C. 371 (c)2)).

7. [] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [] have not been made and will not be made.

8. [] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c) (3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)) (unexecuted).

10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98 (with 2 references).

12. [] An assignment document for recording. A **separate** cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.
    [] A SECOND or SUBSEQUENT preliminary amendment.

14. [] A substitute specification.

15. [] A change of power of attorney an/or address letter.

16. [] Other items or information:

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5/18/01 EL706740622US
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D B Peck
Name (Print)

Signature

JC03 Rec'd PCT/PTO 18 MAY 2001

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.50) 09/856417	INTERNATIONAL APPLICATION NO.: PCT/IL99/00619	Attorney's Docket Number 6727/0G367US0

17. [X] The following fees are submitted:		ALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492 (a)(1)-(5)): Search Report has been prepared by the EPO [] or JPO []	$860.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482)	$690.00		
No international preliminary examination fee paid to USPTO(37 CFR 4.482) but international search fee paid to USPTO (37 CFR 1.445 (a) (2)...	$710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....	$1,000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....	$100.00		$860.00

Surcharge of $130.00 for furnishing the oath or declaration later than []20 []30 months from the earliest claimed priority date (37 CFR 1.492(e)).	ENTER APPROPRIATE BASIC FEE AMOUNT =	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	45 - 20	25	25 X $18.00	$450.00	
Independent Claims	5 - 3	2	2 X $80.00	$160.00	
Multiple dependent claims(s) (if applicable)		+270		$	
			TOTAL OF ABOVE CALCULATIONS =	$1470.00	
Reduction by 1/2 for filing by small entity, if applicable.				$	
			SUBTOTAL =	$1470.00	
Processing fee of $130.00 for furnishing the English translation later the [] 20 [] 39 months from the earliest claimed priority date (37 CFR 1.492(f)).		+		$	
			TOTAL NATIONAL FEE =	$1470.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). the assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property		+		$	
			TOTAL FEES ENCLOSED =	$1470.00	
				Amount to be refunded	$
				charged	$

a. [] A check in the amount of $ to cover the above fees is enclosed.

b. [] Please charge my Deposit Account No.04-0100 in the amount of $ to cover the above fees.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0100. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO
S. Peter Ludwig
Darby & Darby P.C.
805 Third Avenue
New York, New York 10022-7513

SIGNATURE 

NAME **S. Peter Ludwig**

REGISTRATION NO. **25,351**

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Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No: 6727/0J367US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Azariah JOSSIFOFF

Serial No.: TBA (U.S. National Phase of International Application No. PCT/IL99/00619)

Filed: Concurrently Herewith

For: VAGINALLY ADMINISTRATABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

May 18, 2001

Sir:

Prior to examination, please amend this application as follows.

IN THE CLAIMS

Please amend the claims pursuant to 37 C.F.R. 1.121(c)(1)(i) as follows (see the accompanying "marked up" version pursuant to 1.121(c)(1)(i)).

REMARKS

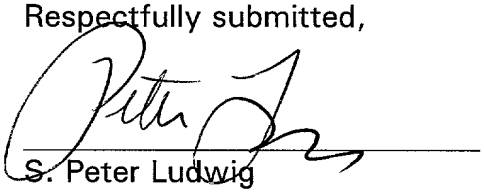
Entry of the foregoing amendments is respectfully requested.

After entry of this amendment, claims 1-45 are pending.

The claims have been amended to eliminate multiple claim dependencies and reduce the filing fees. These are not narrowing amendments.

An early and favorable examination is respectfully requested.

Respectfully submitted,



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6. A method according to claim 3, wherein said third mixture is sieved through sieves having a pore size of between about 400 and 450 microns.

8. A method according to claim I wherein said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size of between about 100 and 150 microns.

10. A method according to claim 3, wherein said first lubricant is silicon dioxide (colloidal anhydrous silica).

11. A method according to claim 3, wherein said material selected from a first filler or a disintegrant is a starch exhibiting good flow properties.

14. A method according to claim 3, wherein said binder which binds dry particles is polyvinylpyrrolidone (povidone).

16. A method according to claim 3, wherein said second filler is derived from a natural source.

18. A method according to claim 3, wherein said first portion and said second portion of said second filler are of generally the same size.

19. A method according to claim 3, wherein said effervescent is prepared prior to said intimate mixing of said first portion of said second tiller with said effervescent.

20. A method according to claim 3, wherein said effervescent is prepared *in situ* as part of said intimate mixing of said first portion of said second filler with said effervescent.

21. A method according to claim 3, wherein said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, to obtain said third mixture.

23. A method according to claim 3, wherein said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns to obtain said fourth mixture.

25. A method according to claim 3, wherein said second lubdicant is selected from

magnesium stearate, talc, sodium lauryl sulfate, and phosphates known in the art to function as lubricants.

27. A method according to claim 3, wherein said material selected from a saponificant or a third lubricant is sodium lauryl sulfate.

28. A method according to claim 2, wherein said effervescent is a mixture of a pharmaceutically acceptable carboxylic or dicarboxylic acid and a pharmaceutically acceptable salt of HCO_3-.

30. A method according to claim 28, wherein said pharmaceutically acceptable salt of HCO_3- is sodium bicarbonate.

31. A method according to claim 28, wherein said pharmaceutically acceptable carboxylic or dicarboxylic acid and said bicarbonate are present in an amount providing a molar excess of -COOH groups.

32. A method according to claim 28, wherein said effervescent comprises a mixture of adipic acid and sodium bicarbonate.

33. A method according to claim 2, wherein said effervescent comprises between about 6 and 10 wt.%.

34. A method according to claim 1 wherein the amount of water mixed with said micronized progesterone is between about 25 and 28 wt.% of the amount of micronized progesterone.

36. A method according to claim 1, wherein said water is added to said micronized progesterone at rate of between about 6 to 9 ml per minute.

37. A method according to claim 1, wherein said water is mixed with said micronized progesterone at a mixing speed of between about 25-33.3 rpm.

38. A method according to claim I wherein said drying of said wetted micronized progesterone is done at a temperature of between about 55°C and about 60°C.

39. A method according to claim 1 wherein all of said mixing steps are carried out at a temperature of between about 15°C and 30°C.

45. A tablet according to claim 43 comprising between about 6 to 8 wt.% effervescent.

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D B Peck — Name (Print)

L Beck — Signature

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Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No: 6727/0J367US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Azariah JOSSIFOFF

Serial No.: TBA (U.S. National Phase of International Application No. PCT/IL99/00619)

Filed: Concurrently Herewith

For: VAGINALLY ADMINISTRATABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME

MARKUP ACCOMPANYING PRELIMINARY AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

May 18, 2001

Sir:

6. A method according to [any of claims 3 to 5] claim 3, wherein said third mixture is sieved through sieves having a pore size of between about 400 and 450 microns.

8. A method according to claim I [any of claims 3 to 7] wherein said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size of between about 100 and 150 microns.

10. A method according to claim 3 [any of claims 3 to 9], wherein said first lubricant is silicon dioxide (colloidal anhydrous silica).

11. A method according to claim 3 [any of claims 3 to 10], wherein said material selected from a first filler or a disintegrant is a starch exhibiting good flow properties.

14. A method according to claim 3 [any of claims 3 to 13], wherein said binder which binds dry particles is polyvinylpyrrolidone (povidone).

16. A method according to claim 3 [any of claims 3 to 15], wherein said second filler is derived from a natural source.

18. A method according to claim 3 [any of claims 3 to 17], wherein said first portion and said second portion of said second filler are of generally the same size.

19. A method according to claim 3 [any of claims 3 to 18], wherein said effervescent is prepared prior to said intimate mixing of said first portion of said second filler with said effervescent.

20. A method according to claim 3 [any of claims 3 to 18], wherein said effervescent is prepared *in situ* as part of said intimate mixing of said first portion of said second filler with said effervescent.

21. A method according to claim 3 [any of claims 3 to 20], wherein said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, to obtain said third mixture.

23. A method according to claim 3 [any of claims 3 to 22] , wherein said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns to obtain said fourth mixture.

25. A method according to claim 3 [any of claims 3 to 24], wherein said second lubricant is selected from magnesium stearate, talc, sodium lauryl sulfate, and phosphates known in the art to function as lubricants.

27. A method according to [any of claims 3 to 26] claim 3, wherein said material selected from a saponificant or a third lubricant is sodium lauryl sulfate.

28. A method according to [any of claims 2 to 27] claim 2, wherein said effervescent is a mixture of a pharmaceutically acceptable carboxylic or dicarboxylic acid and a pharmaceutically acceptable salt of HCO_3-.

30. A method according to claim 28 [or 29], wherein said pharmaceutically acceptable salt of HCO_3- is sodium bicarbonate.

31. A method according to [any of claims 28 to 30] claim 28, wherein said pharmaceutically acceptable carboxylic or dicarboxylic acid and said bicarbonate are present in an amount providing a molar excess of -COOH groups.

32. A method according to [any of claims 28 to 31] claim 28, wherein said effervescent comprises a mixture of adipic acid and sodium bicarbonate.

33. A method according to [any of claims 2 to 32] claim 2, wherein said effervescent comprises between about 6 and 10 wt.%[, preferably about 8 wt.%] of the tablet.

34. A method according to [any of claims 1 to 33] claim 1 wherein the amount of water mixed with said micronized progesterone is between about 25 and 28 wt.% of the amount of micronized progesterone.

36. A method according to [any of claims 1 to 35] claim 1, wherein said water is added to said micronized progesterone at rate of between about 6 to 9 ml per minute.

37. A method according to [any of claims 1 to 36] claim 1, wherein said water is mixed with said micronized progesterone at a mixing speed of between about 25-33.3 rpm.

38. A method according to [any of claims 1 to 37] claim I wherein said drying of said wetted micronized progesterone is done at a temperature of between about 55°C and about 60°C.

39. A method according to [any of claims 1 to 38] claim 1 wherein all of said mixing steps are carried out at a temperature of between about 15°C and 30°C.

45. A tablet according to claim 43 [or 44] comprising between about 6 to 8 wt.% effervescent.

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VAGINALLY ADMINISTRABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME

Field of the Invention

The invention relates to the preparation of pharmaceutical compositions containing progesterone, in particular to compositions for vaginal delivery of progesterone.

Background of the Invention

Since its discovery in the 1950's, synthetic oral progesterone has been used for a variety of gynecological conditions. However, androgenic activity inherent in the synthetic compound precludes its liberal use in assisted reproductive technology (ART) because of the threat of teratogenic effects.

Furthermore, synthetic progesterone used in hormonal replacement therapy (HRT) may partially reverse the estrogenic benefits on the cardiovascular system and lipoprotein metabolism (Lobo, Am. J. Obstet. Gynecol. **166** (1992), 1997-2004; Fahraeus et al., Eur. J. Clin. Invest. **13** (1983), 447-453; Ottosson et al., Am. J. Obstet. Gynecol. **151** (1985), 746-750; Knopp, Am. J. Obstet. Gynecol. **158** (1988), 1630-1643; Crook et al., **166** (1992) 950-954).

Natural progesterone is devoid of any androgenic activity that might compromise lipoprotein metabolism or induce teratogenicity. Moreover, it probably has a direct beneficial effect on blood vessels (Jiang et al., Eur. J. Pharmacol. **211** (1992), 163-167).

The major difficulty in utilizing natural progesterone is its route of administration. Oral intake is hampered by rapid and extensive intestinal and liver metabolism, leading to poorly sustained serum levels and low bioavailability (Adlercreutz et al., J. Steroid Biochem. **13** (1980), 231-244; Arafat et al., Am. J. Obstet. Gynecol. **159** (1988), 1203-1209; Whitehead et al., Brit. Med. J. **280** (1980), 825-827; Ottosson et al., Br. J. Obstet. Gynecol. **91** (1984), 1111-1119; Padwick et al., Fertil. Steril. **46** (1986), 402-407; Nahoul et al., Maturitas **16** (1993), 185-202; Nillus et al., Am. J. Obstet. Gynecol. **110** (1971), 470-477; Chakmakjian et al., J.

Reprod. Med. **32** (1987), 443-448). Intramuscular injection assures reliable absorption, but is painful, can cause local irritation and cold abscesses (Devroey et al., Int. J. Fertil. **34** (1989), 188-193), must be administered by trained medical personnel, and often suffers from low patient compliance.

For these reasons, the vaginal route has become the most established way in which to deliver natural progesterone. The progesterone is easily administered to the vagina, which has a large potential of absorption, and also avoids liver first-pass metabolism when delivered to the vagina.

Many vaginal formulations have been assayed, mostly as suppositories (Price et al., Fertil. Steril. **39** (1983), 490-493; Norman et al., Fertil. Steril. **56** (1991), 1034-1039; Archer et al., Am. J. Obstet. Gynecol., **173** (1995), 471-478), gelatin capsules (Devroey et al., Int. J. Fertil. **34** (1989), 188-193; Smitz et al., Hum. Reprod. **2** (1992), 309-314; Miles et al., Fertil. Steril. **62** (1994), 485-490), and recently as bio-adhesive gels (Fanchin et al., Obstet. Gynecol. **90** (1997), 396-401; Ross et al., Am. J. Obstet. Gynecol. **177** (1997), 937-941).

Although the suppositories are easily inserted, they melt at body temperature and lead to disturbing vaginal discharge. Oral gelatin capsule containing micronized progesterone have also been used vaginally (Devroey et al., Int. J. Fertil. **34** (1989), 188-193; Smitz et al., Hum. Reprod. **2** (1992), 309-314; Miles et al., Fertil. Steril. **62** (1994), 485-490), but insertion of a small capsule high into the vagina is difficult and large doses of 600 to 800 mg are needed to achieve adequate plasma concentration (Smitz et al., Hum. Reprod. **2** (1992), 309-314; Miles et al., Fertil. Steril. **62** (1994), 485-490; Bourgain et al., Hum. Reprod. 5 (1990), 537-543).

U.S. Patents No. 5,084,277 and 5,116,619, both to Greco et al., disclose a process for the preparation of a progesterone-containing tablet and tablets so prepared. The Greco et al. process involves wet granulation of progesterone into the tablets. As is well-known in the art, wet granulation processes necessitate several steps in the formulation of the resulting tablets. These steps add considerably to the production costs of tablets produced by wet granulation methods, particularly in comparison to comparable "direct compaction" methods, in which the material of interest is tabletted while dry and which involve fewer steps than wet-granulation

methods. Greco et al. employs a wet granulation technique because commercially available progesterone has bulk properties which render it unsuitable for direct compaction in the concentrations necessary for use in ART (typically about 50-100 mg progesterone per 1000 mg tablet). Greco gives no suggestion as to how one might be able to tablet progesterone via a direct-compaction method, which is economically more desirable.

The use of a wet granulation method in the preparation of progesterone-containing tablets also precludes incorporation of an effervescent into the tablet. If the tablet is to be vaginally administered, incorporation of an effervescent would be helpful, since the effervescent would aid in the dissolution of the tablet and absorption of the progesterone into the bloodstream.

Summary of the Invention

The present invention seeks to provide a method for the production of a tablet for the vaginal delivery of progesterone as well as tablets containing progesterone.

There is thus provided, in accordance with a preferred embodiment of the invention, a method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

There is also provided. in accordance with another preferred embodiment of the invention, a method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including an effervescent.

There is further provided, in accordance with another preferred embodiment of the invention, a method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

sieving a first lubricant to obtain a sieved first lubricant;

mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing an effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing the fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant;

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and

tabletting said sixth mixture by direction compaction to form a tablet.

In a preferred embodiment of the invention, the amount of water mixed with the micronized progesterone is between about 25 and 28 wt.% of the amount of micronized progesterone.

In another preferred embodiment of the invention, the water is added to the micronized progesterone at rate of between about 6-9 ml per minute, at a mixing speed of between about 25-33.3 rpm.

In another preferred embodiment of the invention, the first lubricant is sieved through sieves having a pore size of between about 400 and 450 microns, preferably about 425 microns.

In another preferred embodiment of the invention, the third mixture is sieved through sieves having a pore size of between about 400 and 450 microns, preferably about 425 microns prior to mixing with the second mixture.

In another preferred embodiment of the invention, said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size

of between about 100 and 150 microns, preferably 125 microns prior to mixing with said fifth mixture.

In one preferred embodiment of the invention, said drying of said wetted micronized progesterone is done at a temperature of between about 55°C and about 60°C.

In another preferred embodiment of the invention, all of said mixing steps are carried out at a temperature of between about 15°C and 30°C.

In one preferred embodiment of the invention, said first lubricant is silicon dioxide (colloidal anhydrous silica).

In another preferred embodiment of the invention, said material selected from a first filler or a disintegrant is a starch exhibiting good flow properties, such as cornstarch 1500 or other starches derived from corn (maize), potatoes or wheat, as are well known in the art.

In a preferred embodiment of the invention, the binder which binds dry particles is polyvinylpyrrolidone (povidone), e.g. Povidone 30.

In another preferred embodiment of the invention, said second filler is derived from a natural source and is more preferably lactose or is composed principally of lactose (e.g. ludipress, which as is well known in the art is a commercially available mixture of polyvinylpyrrolidone and lactose).

In a preferred embodiment of the invention, said effervescent is a mixture of a pharmaceutically acceptable carboxylic or dicarboxylic acid, such as adipic acid or tartaric acid, and a pharmaceutically acceptable salt of HCO_3^-, such as sodium bicarbonate. Preferably the acid and bicarbonate are present in an amount providing a molar excess of -COOH groups.

In another preferred embodiment of the invention, said first portion and said second portion of said second filler are of generally the same size.

In one preferred embodiment of the invention, the effervescent is prepared prior to said intimate mixing of said first portion of said second filler with said effervescent. In another preferred embodiment of the invention, said effervescent is prepared *in situ* as part of said intimate mixing of said first portion of said second filler with said effervescent.

In a preferred embodiment of the invention, said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, preferably about 425 microns diameter to obtain said third mixture.

In a preferred embodiment of the invention, the effervescent comprises between about 6 and 10 wt.%, preferably about 8 wt.% of the tablet.

In one preferred embodiment of the invention, said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, preferably about 425 microns diameter to obtain said fourth mixture.

In a preferred embodiment of the invention, said second lubricant is selected from magnesium stearate, talc, sodium lauryl sulfate, and phosphates known in the art to function as lubricants.

In another preferred embodiment of the invention, said material selected from a saponificant or a third lubricant is sodium lauryl sulfate.

There is also provided in accordance with another preferred embodiment of the invention a tablet prepared by the steps of: slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone; drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone; mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

There is also provided in accordance with another preferred embodiment of the invention a tablet prepared by the steps of: slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone; drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone; mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including an effervescent.

There is also provided in accordance with another preferred embodiment of the invention a tablet prepared by the steps of: slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone,

whereby to obtain wetted micronized progesterone; drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone; sieving a first lubricant to obtain a sieved first lubricant; mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture; mixing a binder which binds dry particles with said first mixture to form a second mixture; intimately mixing an effervescent and a first quantity of a second filler to form a third mixture; sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture; intimately mixing the fourth mixture with a second quantity of said second filler to form a fifth mixture; sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant; intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and tabletting said sixth mixture by direction compaction to form a tablet.

There is also provided in accordance with a preferred embodiment of the invention a tablet comprising between about 6 to 20 wt.% progesterone and between about 5 to 12 wt.% effervescent. In a preferred embodiment of the invention, the tablet comprises between about 8 to 12 wt.% progesterone. In a preferred embodiment of the invention, the tablet comprises between about 6 to 8 wt.% effervescent.

Detailed Description of the Preferred Embodiments

The invention will be better understood through the following illustrative and non-limitative description and examples of preferred embodiments of the invention.

Example 1

Preparation of Tablets

Step 1: To 1000 g of micronized progesterone were added 280 g of distilled water, with mixing using a planetary mixer, over a period of 30 minutes. After

mixing, the wetted micronized progesterone was spread on pans to thickness of about 4-5 mm, and the pans then placed in an oven at 58°C. The humidity was checked periodically using a humidity checker. When the humidity of the micronized progesterone was reduced to substantially 0%, the dried micronized progesterone was either used immediately in step 2 as described below, or was stored in dry, sealed containers for later use in step 2.

Step 2: Colloidal anhydrous silica (Aerosil 380, 25 g) was sieved through a Russel sieve having pores of 425 micron size, and mixed for 10 minutes with 1000 g of micronized progesterone from Step 1 and 2100 g of maize 1500 starch, using an Angelsman mixer at 32 RPM, to form Mixture A. At the end of the 10 minutes of mixing, 490 g of povidone 30 were added to Mixture A, and mixing was continued for another ten minutes, to prepare "Mixture B".

Step 3: Lactose (Ludipress, BASF, 3800 g), adipic acid (570 g) and sodium bicarbonate (430 g) were mixed for 10 minutes at room temperature using an Angelsman mixer at 32 RPM. Following mixing, these ingredients were sieved through a Russel sieve having pores of 425 microns to obtain "Mixture C".

Step 4: Mixtures B and C were mixed for 10 minutes at room temperature using an Angelsman mixer at 32 RPM to obtain "Mixture D".

Step 5: Mixture D (8415 g) was mixed with 3800 g of lactose (Ludipress) for 10 minutes at room temperature using an Angelsman mixer at 32 RPM, to obtain "Mixture E".

Step 6: Magnesium stearate (230 g) and sodium lauryl sulfate (50 g) were sieved through a Russel sieve (pore size 125 microns). The sieved magnesium stearate and sodium lauryl sulfate were then mixed for with mixture E for 20 minutes at room temperature using an Angelsman mixer, to obtain "Mixture F".

Step 7: Tablets were obtained from mixture F by direct compaction using an Eko Korsch Press. The amounts of ingredients listed in this example are suitable for production of 10,000 tablets each containing about 100 mg progesterone.

Example 2

Using the above process, tablets of 1187 mg to 1312 mg total weight, containing from 90 to 110 mg progesterone, were obtained.

Example 3

The process described in Example 1 was modified by doubling the amount of filler (Ludipress) to obtain tablets containing on average 50 mg progesterone.

Example 4

The pharmacokinetics and clinical use of tablets prepared in accordance with the invention were evaluated as follows: 50 healthy, post-menopausal women with intact uteri, 39 of whom had suffered premature menopause and 11 who were truly postmenopausal, all of whom were undergoing hormone replacement therapy (HRT), submitted blood samples for determination of baseline profiles of hormones (progesterone and other hormones) and other biochemicals (bilirubin, cholesterol, etc.). The blood samples were taken at 8 AM on the first day of the evaluation (day 0) in a fasting state, by intravenous indwelling catheter which was introduced into the cubital vein. Non-estrogen primed postmenopausal women were chosen in order to avoid confusion with endogenous progesterone secretion and estrogen influence on vaginal mucosa absorption (Villanueva et al., Fertil. Steril. **35** (1981), 433-437).

The women then self-administered the progesterone vaginal tablet using a plastic applicator and lay down for 20 minutes. Repeat blood samples for progesterone concentration were withdrawn 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours after the vaginal insertion. Blood was allowed to clot at room temperature for 1 hour, after which the serum was separated by centrifugation and stored at -20°C until analysis.

To evaluate clinical use of the drug, the women were instructed to insert tablets prepared in accordance with the present invention, containing the same dose as administered on day 0, twice daily starting on day 1, and to recline for 20 minutes after each insertion. On days 14 and 30, blood samples for comparison with the baseline were drawn in the morning while the subjects were in a fasting state.

Of the 50 women who participated in the evaluation, 20 were allocated tablets containing 50 mg progesterone, and the remainder of the participants received tablets containing 100 mg progesterone. The baseline details of the participants are summarized in Table I.

Table I

	Tablets containing 50 mg progesterone	Tablets containing 100 mg progesterone	Total
Median age (years)	43 ± 6.1	43.2 ± 7.9	43.3 ± 7.2
Age range (years)	28-53	28-55	28-55
Height (cm)	161.3 ± 8.6	161.6 ± 5.7	161.5 ± 6.9
Weight (kg)	67.1 ± 11.5	62.8 ± 13.1	64.5 ± 12.5
BMI (kg/m^2)	25.9 ± 4.2	24.0 ± 4.4	24.8 ± 4.4

Data are expressed as mean ± standard deviation unless otherwise specified. Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters.

A single vaginal application of a 50 mg progesterone-containing tablet prepared in accordance with the invention resulted in the rapid increase of plasma progesterone concentration. The mean peak plasma level (T_{max}), mean elimination half-life ($T_{1/2}$), maximal serum concentration (C_{max}), and AUC (area under the curve, i.e. total amount of plasma progesterone observed) derived from the blood samples taken on day 0 of the evaluation are summarized in Table II.

Table II

	Progesterone dose	
	50 mg (20 subjects)	100 mg (30 subjects)
T_{max} (hours)	6.1 ± 2.63	6.4 ± 3.35
$T_{1/2}$ (hours)	13.18 ± 1.3	13.7 ± 1.05
C_{max} (nmol/liter)	20.43 ± 8.01	31.61 ± 12.62[a]
AUC (nmol/hour/liter)	154.15 ± 60.31	247.61 ± 123.04[b]

Values are mean ± standard deviation; [a] $P = 0.0004$; [b] $P = 0.001$.

As shown in Table III, after 14 and 30 days of continuous application twice daily, the serum P levels were significantly higher compared to baseline values on day 0. No statistically significant difference in plasma levels of follicle stimulating hormone, leutinizing hormone, estradiol, cortisol, dehydroepiendosterone sulfate, or aldosterone were observed in the study groups between baseline values and after continued administration of the tablets of the invention. Similarly, the plasma levels of serum glutamic oxaloacetic transaminase, alkaline phosphatase, cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and very low density lipoprotein did not change significantly between the baseline measurement and the measurements at 14 and 30 days of twice-daily administration.

Table III

Blood Progesterone levels, nmol/liter

Day sample was taken	Progesterone dose	
	50 mg (20 subjects)	100 mg (30 subjects)
Day 0[a]	1.05 ± 0.7	3.0 ± 2.4
Day 14[a]	17.48 ± 9.8[b]	26.08 ± 13.96[b]
Day 30[a]	17.38 ± 14.39	21.42 ± 16.32

[a] $P = 0.0001$, significant difference between progesterone baseline values on day 0 compared to day 14 and day 30, [b] $P = 0.02$.

Example 5

The efficacy of tablets prepared in accordance with the present invention was compared with the efficacy of prior art tablets as follows:

Thirteen healthy, postmenopausal women with intact uteri who were undergoing hormonal replacement therapy (HRT) were given complete medical evaluation by history, physical and gynecological examination, and instructed to discontinue HRT two weeks prior to the comparative trial.

Part A: Single-dose pharmacokinetics of micronized progesterone in the form of a gelatin capsule (Utrogestan, produced by Basins-Iscovesco, Paris, France). Participants received oral ethinyl estradiol (Estrofem, Novo-Nordisk, Denmark), 4 mg per day for 14 days. On day 14 at 8 AM, in a fasting state, an intravenous indwelling catheter was inserted into the cubital vein and blood was drawn for baseline

progesterone and estrogen levels. The women were then instructed to self-administer a single gelatin capsule containing 100 mg of micronized progesterone high in the vagina. Repeat blood samples for progesterone concentrations were drawn 1/2, 1, 2, 4, 6, 8, 10, 12 and 24 hours after the vaginal insertion.

Part B: Single-dose pharmacokinetics of micronized progesterone in the form of a vaginal tablet according to the present invention. After a washout period of 2 weeks, the same subjects as in Part A were again administered 4 mg or ethinyl estradiol (Estrofem) for 14 days. On day 14 the same procedure as recited in Part A was repeated, except that this time the women were instructed to insert 100 mg of progesterone in the form of an effervescent tablet according to the present invention, using a plastic applicator. Blood samples for progesterone levels were drawn at the same intervals as in Part A.

Samples were assayed using an Immulite enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA) to measure plasma progesterone (SI conversion factor 3.18; sensitivity 0.2 ng/ml (0.6 nmol/L, inter- and intra-assay coefficients of variation precision <10%)) and estradiol (E_2) (SI conversion factor 3.67; sensitivity 12 pg/ml (44 pmol/L, inter- and intra-assay coefficients of variation precision <10%). The pharmacokinetic parameters calculated from the concentration curve were compared between the two study groups by the Wilcoxon 2-sample test, the Kruskal-Wallis test and by analysis of variance (ANOVA). Students T-test was used to compare estrogen levels for the two treatment parts.

Table IV summarizes the baseline details of the of the thirteen women who participated in the study of Example 5.

Table IV

	Mean ± SD	Median	Minimum	Maximum
Age (years)	52.2 ± 3.6	53	42	57
Weight (kg)	72 ± 15.4	70	46	100
Height (cm)	165.1 ± 6.5	165	155	178
BMI (kg/m^2)	263. ± 4.7	25.7	19.1	34.2

Data are expressed as mean ± standard deviation unless otherwise specified. Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters.

The mean peak plasma level (T_{max}), mean elimination half-life ($T_{1/2}$), maximal serum concentration (C_{max}), and AUC (area under the curve, i.e. total amount of plasma progesterone observed) derived from the blood samples taken on day 0 of the evaluation are summarized in Table V.

Table V

	Treatment	
	Vaginal Tablet	Gelatin Capsule
Tmax (hours)	6.92 ± 3.12	6.23 ± 6.56[b]
$T_{1/2}$ (hours)	16.39 ± 5.25	22.08 ± 16.5
C_{max} (nmol/l)	31.53 ± 9.15	23.85 ± 9.57[a]
AUC (nmol/h/l)	379.99 ± 137.07	325.89 ± 167.78

Values are mean ± standard deviation, [a] $P = 0.0472$; [b] Statistically significant difference of variance, $P = 0.02$.

A single dose of 100 mg micronized progesterone in the form of both gelatin capsules and vaginally administrable tablets in accordance with the present invention resulted in a similar rapid increase in plasma progesterone levels within 2.5-3 hours after administration. The statistically significant difference of variance between the two groups indicates a more predictable T_{max} for the tablets of the present invention than for the prior art gelatin capsules.

It is to be understood that the amounts and proportions of ingredients recited in the foregoing examples are illustrative only, and that these amounts and proportions may be varied within the scope of the invention. For example, the Example 1 the amount of effervescent recited is about 8 wt.% of the tablets which are the final product of the process described in Example 1. However, the effervescent may be omitted in the practice of the invention, or it may be included in an amount of up to about 12 wt.% of the tablet. Preferably the effervescent constitutes between about 5-12 wt.%, more preferably between about 6-8 wt.% of the tablet. Similarly, progesterone may constitute up to about 20 wt.% of the tablet, preferably between about 6-20 wt.%, more preferably between about 8-12 wt.% of the tablet.

It will be appreciated that various features of the invention which are, for clarity, described in the contexts of separate embodiments may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment may also be provided separately or in any suitable subcombination.

It will also be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the invention is defined only by the claims which follow:

CLAIMS

1. A method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

2. A method according to claim 1 for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including said effervescent.

3. A method according to claim 2 for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

sieving a first lubricant to obtain a sieved first lubricant;

mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing an effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing said fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant;

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and

tabletting said sixth mixture by direction compaction to form a tablet.

4. A method according to claim 3, wherein said first lubricant is sieved through sieves having a pore size of between about 400 and 450 microns.

5. A method according to claim 4, wherein said first lubricant is sieved through sieves having a pore size of about 425 microns.

6. A method according to any of claims 3 to 5, wherein said third mixture is sieved through sieves having a pore size of between about 400 and 450 microns

7. A method according to claim 6, where said pore size is about 425 microns.

8. A method according to any of claims 3 to 7 wherein said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size of between about 100 and 150 microns.

9. A method according to claim 8, wherein said pore size is about 125 microns.

10. A method according to any of claims 3 to 9, wherein said first lubricant is silicon dioxide (colloidal anhydrous silica).

11. A method according to any of claims 3 to 10, wherein said material selected from a first filler or a disintegrant is a starch exhibiting good flow properties.

12. A method according to claim 11 wherein said starch is derived from corn (maize), potatoes or wheat.

13. A method according to claim 12 wherein said starch is cornstarch 1500.

14. A method according to any of claims 3 to 13, wherein said binder which binds dry particles is polyvinylpyrrolidone (povidone).

15. A method according to claim 14, wherein said binder which binds dry particles is Povidone 30.

16. A method according to any of claims 3 to 15, wherein said second filler is derived from a natural source.

17. A method according to claim 16, wherein said second filler is selected from lactose or a composition composed principally of lactose.

18. A method according to any of claims 3 to 17, wherein said first portion and said second portion of said second filler are of generally the same size.

19. A method according to any of claims 3 to 18, wherein said effervescent is prepared prior to said intimate mixing of said first portion of said second filler with said effervescent.

20. A method according to any of claims 3 to 18, wherein said effervescent is prepared *in situ* as part of said intimate mixing of said first portion of said second filler with said effervescent.

21. A method according to any of claims 3 to 20, wherein said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, to obtain said third mixture.

22. A method according to claim 21, wherein said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size of about 425 microns diameter to obtain said third mixture.

23. A method according to any of claims 3 to 22, wherein said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is

accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns to obtain said fourth mixture.

24. A method according to claim 23, wherein said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size of about 425 microns diameter to obtain said fourth mixture.

25. A method according to any of claims 3 to 24, wherein said second lubricant is selected from magnesium stearate, talc, sodium lauryl sulfate, and phosphates known in the art to function as lubricants.

26. A method according to claim 25, wherein said lubricant is magnesium stearate.

27. A method according to any of claims 3 to 26, wherein said material selected from a saponificant or a third lubricant is sodium lauryl sulfate.

28. A method according to any of claims 2 to 27, wherein said effervescent is a mixture of a pharmaceutically acceptable carboxylic or dicarboxylic acid and a pharmaceutically acceptable salt of HCO_3^-.

29. A method according to claim 28, wherein said pharmaceutically acceptable carboxylic or dicarboxylic acid is selected from adipic acid or tartaric acid.

30. A method according to claim 28 or 29, wherein said pharmaceutically acceptable salt of HCO_3^- is as sodium bicarbonate.

31. A method according to any of claims 28 to 30, wherein said pharmaceutically acceptable carboxylic or dicarboxylic acid and said bicarbonate are present in an amount providing a molar excess of -COOH groups.

32. A method according to any of claims 28 to 31, wherein said effervescent comprises a mixture of adipic acid and sodium bicarbonate.

33. A method according to any of claims 2-32, wherein said effervescent comprises between about 6 and 10 wt.%, preferably about 8 wt.% of the tablet.

34. A method according to any of claims 1 to 33 wherein the amount of water mixed with said micronized progesterone is between about 25 and 28 wt.% of the amount of micronized progesterone.

35. A method according to claim 34, wherein the amount of water mixed with said micronized progesterone is about 28 wt.% of the amount of micronized progesterone.

36. A method according to any of claims 1 to 35, wherein said water is added to said micronized progesterone at rate of between about 6 to 9 ml per minute.

37. A method according to any of claims 1 to 36, wherein said water is mixed with said micronized progesterone at a mixing speed of between about 25-33.3 rpm.

38. A method according to any of claims 1 to 37 wherein said drying of said wetted micronized progesterone is done at a temperature of between about 55°C and about 60°C.

39. A method according to any of claims 1 to 38 wherein all of said mixing steps are carried out at a temperature of between about 15°C and 30°C.

40. A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

41. A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including said effervescent.

42. A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting

capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

sieving a first lubricant to obtain a sieved first lubricant;

mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing an effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing said fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant;

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and

tabletting said sixth mixture by direction compaction to form a tablet.

43. A tablet comprising between about 6 to 20 wt.% progesterone and between about 5 to 12 wt.% effervescent.

44. A tablet according to claim 43 comprising between about 8 to 12 wt.% progesterone.

45. A tablet according to claim 43 or 44 comprising between about 6 to 8 wt.% effervescent.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY DOCKET NUMBER
6727/0J367US0

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for and which a patent is sought on the invention entitled:

VAGINALLY ADMINISTRATABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME

the specification of which (check only one item below):

[] is attached hereto.

[] was filed as United States application

Serial No. _____

on _____

and was amended

on _____ (if applicable).

[X] was filed as PCT international application

Number PCT/IL99/00619

on November 17, 1999

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Israel	127129	November 18, 1998	[X] YES []NO
			[] YES [] NO
			[] YES [] NO
			[] YES [] NO
			[] YES [] NO

US

Combined Declaration for Patent Application and Power of Attorney (Continued) (Includes Reference to PCT International Applications)	ATTY'S DOCKET NUMBER 6727/0J367US0

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S APPLICATIONS		STATUS (Check one)		
U.S APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO	PCT FILING DATE	U S SERIAL NUMBER ASSIGNED (if any)			
PCT/IL99/00619	Nov. 17, 1999				

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. Morris Relson #15,108, Gordon D. Coplein #19,165, William F. Dudine, Jr. #20,569, Michael J. Sweedler #19,937, S. Peter Ludwig #25,351, Paul Fields #20,298, Joseph B. Lerch #26,936, Melvin C. Garner #26,272, Ethan Horwitz #27,646, Beverly B. Goodwin #28,417, Adda C. Gogoris #29,714, Bert J. Lewen 19,407, Henry Sternberg #22,408, Peter C. Schechter #31,662, Robert Schaffer #31,194,Robert C. Sullivan, Jr. #30,499, and Joseph R. Robinson #33,448, David Leason #36,195, Paul F. Fehlner #35,135, Scott G. Lindvall #40,325, Ira J. Levy #35,587, Marc S. Gross #19,614, and Walt T. Zielinski #18,902

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DR. Jossiffe		
DATE 3.7.01	DATE	DATE